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DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

445

Food and Drug Administration
Denver District Office
Building 20 - Denver Federal Center
P. O. Box 25087
Denver, Colorado 80225
TELEPHONE: 303-236-3000

12-41

September 22, 1997

**WARNING LETTER**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Dr. William R. Lance, D.V.M.
President
Wildlife Pharmaceuticals, Inc.
1401 Duff Drive, Suite 700
Fort Collins, CO 80524

Dear Dr. Lance:

During an inspection of your veterinary drug manufacturing facility conducted July 29 through August 25, 1997, Investigator Grace E. McNally and Microbiologist Diane M. Sprague found significant deviations from the Good Manufacturing Practice regulations for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, Part 211). Such deviations cause veterinary drugs manufactured at this facility to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Deviations noted during the inspection included, but were not limited to the following:

1. Failure to establish control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of the drug product as required by 21 CFR 211.110(a). For example:

   - There is no master validation plan addressing all aspects of your small volume parenteral manufacturing operation.

   - There is no validation protocol for the manufacturing process for Trexonil, Naltrexone HCL Injection, 20 ml.

   - Batch records for the last [redacted] lots of Trexonil produced revealed deviations from the specified process including addition of more active ingredient than specified; variations from lot to lot in mixing/dissolving times for excipients and active ingredients; and failure to perform the proper number of fill volume checks.

2. Failure to maintain master production and control records which accurately reflect the complete manufacturing and control instructions, sampling and testing procedures, and specifications as required by 21 CFR 211.186(b)(9). For example:

   - The master formula does not address mixing times and volumes for the 20L batch sizes, and the mixing times listed for the 10L batch size are not representative of actual practice.

   - Instructions are not consistent with actual practice or in some cases contradictory.

3. Failure to maintain batch production and control records which reflect an accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed as required by 21CFR 211.188(a). For example:

   - Batch records with the same revision date contained different information.

   - Informal and unapproved changes are made to the batch records.

   - Batch records do not reflect sampling of the bulk product for bioburden.

4. Failure to assure that the ventilation and air filtration systems, including prefilters and particulate matter air filters, are appropriate for the air supplies to production areas as required by 21 CFR 211.46(c). For example:

   - There are no HEPA filters or high efficiency filters in the air handling system which supplies air to the class 10,000 and class 100,000 rooms (hallway, formulation room, gowning room, and entry room). Records show that particle counts in the gowning area have exceeded the class 10,000 specification on several occasions.

   - There is no mechanism for monitoring air pressure differentials between the critical class 100 biobubble room and the controlled areas mentioned above.

5. Failure to maintain control of components, including records of disposition as required by 21 CFR 211.80(d). For example raw material inventory records are not consistently maintained. The quantity of ingredient, and the lot number for which it was issued, is not always recorded.

6. Failure to thoroughly investigate unexplained discrepancies (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in the master production and control records) as required by 21 CFR 211.192. For example, a complete investigation was not performed for an out of specification yield result of 2.76% even though the master production record specifies a complete investigation if yield is over/under more than 2.5%. Additionally, there is no documented investigation following the rejection of 43 vials from a [redacted] vial lot of Naltrexone due to particulates.

The above is not intended to be an all-inclusive list of violations. As a manufacturer of veterinary drugs, you are responsible for assuring that your overall operation and the products you manufacture and distribute are in compliance with the law.

You should take prompt action to correct these violations and to establish procedures to prevent their recurrence. Failure to promptly correct these violations may result in regulatory action without further notice, such as seizure and/or injunction.

You should notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Also include copies of any available documentation demonstrating that corrections have been made.

Your response should be sent to the Food and Drug Administration, Denver District Office, Attention: H. Tom Warwick, Acting Compliance Officer.

Sincerely,

Gary C. Dean
District Director